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(71)(72) Applicant and Inventor: KETHARANATHAN, Vettivetpillai [AU/AU]; 132 Barkers Road, Hawthorn, VIC 3122 (AU).

(74) Agent: GRIFFITH HACK & CO.; 509 St Kilda Road, Melbourne, VIC 3001 (AU).

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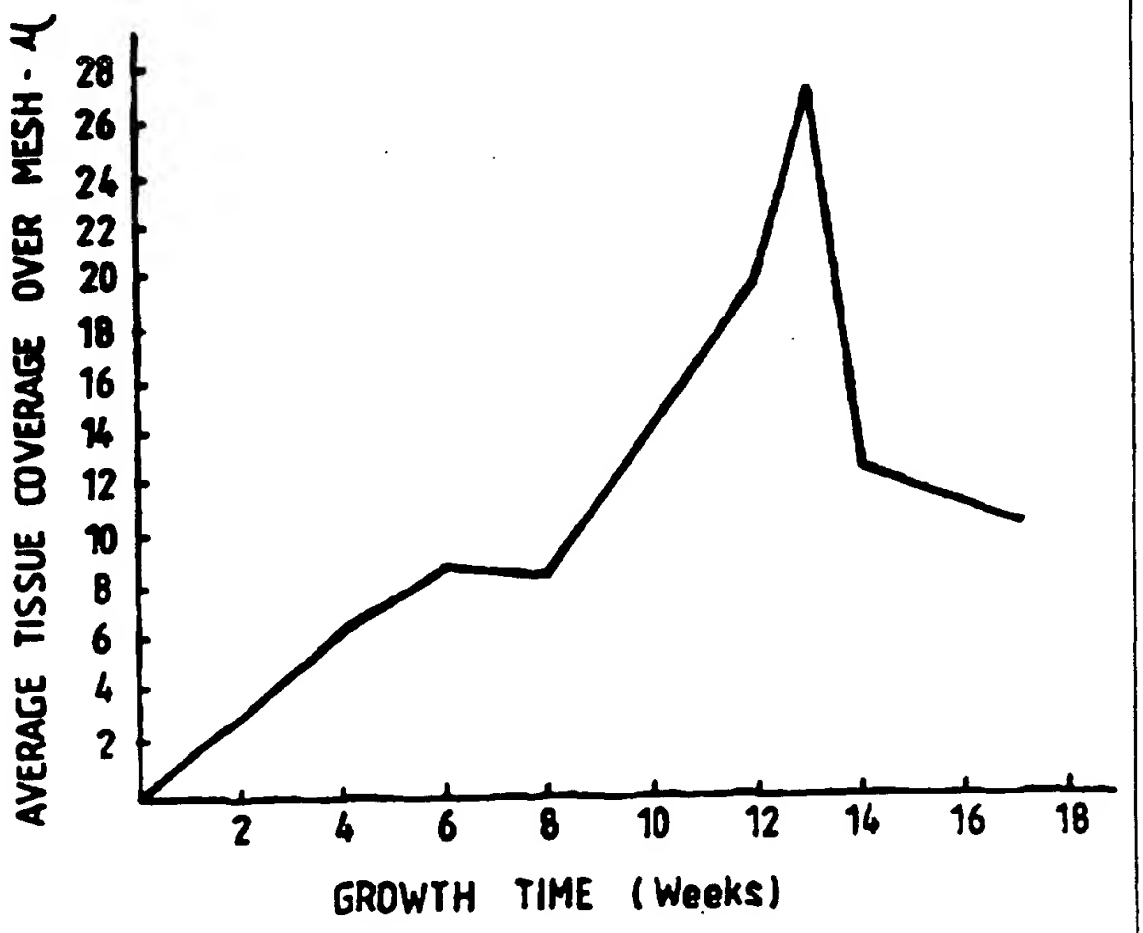
(57) Abstract

A biomaterial is provided which is suitable for use in surgery in a human patient. It comprises a coherent layer of non-human collagenous tissue which has been subjected to glutaraldehyde tanning so as to comprise cross-linked collagen fibrils, and a reinforcement of synthetic material embedded within the coherent layer. The synthetic material has structure features for promoting said embedding, the average density of said features being in situ greater than 50 per square centimetre. Improvements are also provided in a method of producing biomaterials by allowing collagenous tissue growth on mesh structures covering support surfaces implanted into host animals. In one aspect a tubular synthetic fibre mesh structure fits loosely over a support rod or tube, and in the other aspect a sheet support is used and the tissue growing around the sheet support is adapted to form a pocket, pouch or envelope of collagenous material.



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SURGICAL PR STHESES

This invention relates to the field of surgery and more particularly to prosthetic grafts for vascular and non-vascular applications.

US Patent 4,319,363 discloses a prosthesis for revascularisation made from a biomaterial and it describes a method for making the prosthesis in which a mesh covered silicon rod (mandril) is inserted into a living host animal, preferably a sheep, collagenous tissue is allowed to grow around the mandril for about twelve to fourteen weeks after which the implant is removed and subjected to glutaraldehyde tanning to form a prosthesis for revascularisation.

The current invention is based on the surprising discovery that certain variations in the structure, geometry and quantity of the synthetic material or substrate on which it is supported promote improved tissue growth and/or allow the creation of new biological composite materials ("biomaterials") suitable for both vascular and non-vascular surgical application.

In accordance with a first broad aspect of the invention there is provided a biomaterial suitable for use in surgery in a human patient, comprising:

a coherent layer of non-human collagenous tissue which has been subjected to glutaraldehyde tanning so as to comprise cross-linked collagen fibrils, and

a reinforcement of synthetic material embedded within the coherent layer, said synthetic material having structure features for promoting said embedding the average density of said features being in situ greater than 50 per square centimetre.

Preferably, th density of said features is greater than

100 per squar centim tr .

Preferably also, the synthetic material is a fibre mesh and the features for promoting said embedding are the reticulations of the mesh. The fibre mesh may be constructed from polyester yarn. The polyester yarn may also be augmented with polyurethane, either in the form of strands of polyester dipped in polyurethane or strands of polyurethane woven around strands of polyester.

Alternatively, the synthetic material may be particulate in nature, in which case said features may be constituted by individual particles of that material.

Preferably further, the biomaterial is in the shape of a tube. Alternatively, the biomaterial is in the form of sheet.

Preferably also, the biomaterial is smooth on one side to inhibit attachment to surfaces in the patient proximate said one side and rough on the other side to encourage said attachment.

In the case where the synthetic material is a mesh, the mesh may be embedded in the coherent layer such that the mesh structure is in a loose unstretched state.

In accordance with a second broad aspect of the invention there is provided a method of producing a biomaterial, comprising the steps of:

positioning a tubular synthetic fibre mesh structure about a support rod or tube;

implanting the mesh covered support rod or tube in the body of a living, non-human, host animal at such location as to cause growth of collagenous tissue thereon;

allowing said collag nous tissu to grow on the implant until there is formed a coherent wall of said

tissue encompassing th rod or tube and having the mesh structure embedded therein;

removing the implant and said coherent wall of collagenous tissue from the body of the host animal;

subjecting said coherent wall of collagenous tissue to glutaraldehyde tanning in order to produce cross-linking of collagen fibrils therein so as to increase the strength of the wall and also to impart immunological inertness and sterility thereto; and

removing the rod or tube from within the coherent wall of collagenous tissue at any time subsequent to removal of the rod or tube and coherent wall of collagenous tissue from the body of the host animal;

wherein the tubular synthetic fibre mesh structure fits loosely over the support rod.

Optionally, the tubular mesh may be substantially larger in a longitudinal direction than the support rod or tube.

The tubular biomaterial thereby produced may if desired be cut length-wise to produce a sheet.

In accordance with a third broad aspect of the invention there is provided a method of producing a biomaterial, comprising the steps of:

implanting a sheet support in the body of a living, non-human, host animal at such a location as to cause growth of collagenous tissue thereon;

allowing said collagenous tissue to grow on the implant until there is formed a coherent layer of said tissue on both sides of the sheet support;

removing the implant and said coherent layer of collagenous tissue from the body of the host animal;

subjecting said coherent layer of collagenous tissue to glutaraldehyde tanning in order to produce cross-linking of collagen fibrils ther in so as to increase the strength of th layer and also to impart immunological

inertn ss and st rility th reto; and

separating the sheet support from the coherent layer of collagenous tissue at any time subsequent to removal of the implant from the body of the host animal to form a pocket, pouch or envelope of collagenous material.

Preferably, a synthetic material having structure features for promoting embedding of the synthetic material within the collagenous tissue is positioned on the support sheet so as to encompass both sides of the support sheet.

Preferably also, the synthetic material is a mesh structure. The synthetic material may have the features required for the first broad aspect of the current invention. The positioning of the synthetic material may be in accordance with the second broad aspect of the invention.

Preferably, for all first, second and third aspects of the invention, the host animal is a sheep. Preferably too, the implant is made beneath the cutaneous muscle of the lateral thoracic wall of the host animal. Preferably further, the implant is allowed in the host animal for at least ten weeks. Preferably also, the tanning step is carried out by immersing the implant and wall of tissue in a bath of buffered glutaraldehyde after removal of the body of the host animal and before removal of the support or tube. Preferably further, the biomaterial is rehydrated for use using heparin.

In order that the invention may be more clearly understood preferred embodiments of the current invention will be described with reference to the accompanying tables and figures, where:

Figure 1 shows typical tissue growth over the implanted rod or tube overtime f r one embodiment of the inventi n.

Figure 2 illustrat s four variati ns in th structure of polyester mesh used in variati ns II, III and IV of the invention described hereunder. Variation I shown in Figure 2 is the mesh structure used in US Patent 4,319,363.

Figure 2a shos a knotting configuration for Variations I, II ,III ,IV.

Figure 3 is a scanning electron microscope (x 52) magnification of the fibre structure in variation III of Figure 2.

Figure 4 is a reproduction photomicrograph (H & E x 40) showing a section through the pre-flow of variation I, as used in US Patent 4,319,363.

Figure 5 is a similar diagram to Figure 4 (H & E x 40) for variation II of the current invention.

Figure 6 is similar to Figure 4 for variation III of the current invention.

Figure 7 is similar to Figure 4 for variation IV of the invention described hereunder.

Figure 8 is similar to Figure 4 for variation V of the invention described hereunder.

Figure 9 is similar to Figure 4 for variation VI of the invention described hereunder.

Figure 10 is an angiogram of a variation III prosthesis in the below knee femoropopliteal position in the human passing across the bent knee.

Figure 11a is an explanted variation II prosthesis after seven months in the aorta-iliac position in a canine patient.

Figure 11b is a reproduction photomicrograph of a section through the prosthesis of Figure 11a, SR X 10

Figure 12a is a explanted variation II prosthesis similar to Figure 11a after four years in a canine host.

Figure 12b is a reproduction photomicrograph of a section through the prosthesis of Figure 12a, SR X 10.

Figur 13 is a reproduction phot micrograph of a section through a variation III prosth sis after six months

in th aorta-iliac in a canine host, H & E x 40.

Figure 14a shows the cumulative patency of 73 variation I prosthesis in the femoropopliteal position.

Figure 14b shows the primary and secondary cumulative patency of 66 variation II prosthesis evaluated by the same surgical unit as shown in Figure 14a.

Figure 14c shows the primary and secondary patency in the study undertaken by the same surgical unit as in Figure 14a on 79 variation III prosthesis.

Figure 15a shows a wide diameter prosthesis suitable for production of a flat sheet after removal from the host animal.

Figure 15b shows the prosthesis of Figure 15a cut longitudinally and laid flat ready for processing.

Figure 16 shows various shapes of prosthesis which can be produced for different applications such as ligaments.

Figure 17 shows a "bladder" prosthesis suitable for lining an artificial heart, produced in accordance with an embodiment of the invention.

Figure 18 shows an oval shaped patch on its rough side, suitable for body wall patching.

Figure 19 is a scanning electron micrograph at 400 times magnification demonstrating cracking of tissue in variations I and II.

The best method of implementing the improvements the subject of the current invention is to implant the prosthesis in sheep of the following characteristics:

1. Wethers of Border Leicester First Cross, Corriedale, Merino or Polywarth type or any cross breeds of these breeds.
2. Age not less than 3 years and not more than 6 years.
3. Crown to rump length not less than 1 metre.
4. At implant weight n t less than 45 kgs.
5. At explant a w ight gain of 3 to 5 kgs.

The biomaterial is explanted between 12 and 14 weeks. With reference to Figure 1, it can be seen that the maximum tissue coverage occurs at this time.

In the above conditions, sheep provide sterile, self-regulating culture conditions suitable for the reliable and reproducible production of the biomaterial.

Variation I shown in Figure 2 is the prior art polyester mesh of US Patent 4,319,363.

The different meshes of variations I, II, III and IV were knitted on a Raschel Warp knitting machine with a 2-needle bed and 4-bar structure. The knitted loop structure for each variation was designated as shown in Figure 2a. The yarn in each case comprised bundles of approximately 50 polyester strands, each strand being composed of two 44 decitex filaments. The resultant yarn density was 0.6 to 0.8 grammes per metre.

In variations V and VI (not demonstrated) woven polyester mesh was dipped in polyurethane in V and polyurethane strands were wound around polyester strands in VI. The mesh weave of variation III is illustrated in Figure 3.

Modifications in the mandril-mesh assembly influences the eventual tissue incorporation and form. For instance in U.S. 4,319,363, mandril diameter and tubular mesh diameter were identical and the polyester mesh was stretched over the mandril. Illustrating the second aspect of the invention, in variation III an 8 mm diameter tubular mesh was used on a 6 mm diameter mandril. Tubular mesh 106 cm in length was used on a mandril 75 cm in length. This resulted in a thicker and more even cover of tissue over the flow surface without exposed mesh bundles which probably caused less than optimal results in variation I.

In Figures 4, 5, 6, 7, 8 and 9, reproduction photomicrographs of the histology sections of mesh variations I, II, III, IV, V and VI demonstrate the changes in tissue configuration and thickness which occurs with the mesh and mesh/mandril modifications. The tissue cover on the flow surface covering the mesh has increased with each variation and the collagenous tissue has become more compact.

The prior art variation I shown in Figure 4 shows that polyester mesh strands are in bundles (M) supporting a delicate collagen tissue membrane (C). There is a smooth lining to the flow surface (FS) with a thin tissue cover over the mesh bundles.

By contrast, the section through the pre-flow variation II shown in Figure 5 shows polyester mesh bundles (M) closer together due to the increased reticulation density and collagen tissue more compact (C). There is smooth lining to the flow surface (FS) and the tissue cover over the mesh bundles remains thin, as in variation I.

In variation III shown in Figure 6, the polyester mesh bundles (M) are completely incorporated within the collagenous tissue (C) which is very compact. The mesh bundles are slightly closer again, and the flow surface (FS) remains smooth. The tissue cover over the flow surface is thick. This is due to the looseness of the fitting of the mesh over the mandril which allows more tissue to invade the space between the mesh and the mandril compared to the stretched mesh configuration of variation I.

The section through the pre-flow variation IV as shown in Figure 7, shows that the polyester and polyurethane mesh bundl s (M) are well incorporated into the dense collagen tissu (C). The m sh bundles are very closely aligned.

Th strength imparted by the thickness of the tissue cover and cl sely aligned mesh bundl s indicat a non-vascular application for this variation would be appropriate.

With reference to Figure 8 where variation V is shown, the polyester mesh bundles are dipped in polyester (M) and are closely aligned and well incorporated into the collagen tissue (C).

With reference to Figure 9 where variation VI is demonstrated, the polyurethane strands wound around the polyester mesh (M) result in bundles which are well incorporated into the dense collagen tissue (C). The physiochemical characteristics obtained with variation I have been retained in variations II and III with some notable differences listed in Table 1 below.

Table 1.

In vitro studies which demonstrate the improved characteristics of variation III.

Study	Variation II	Variation III
Haemocompatibility (Platelet consumption - The lower the number the more haemocompatible).	16.44 +/- 7.3	10.36 +/- 7
Extension	2.77 +/= .68	5.71 +/- 2.32
Kink radius (The lower the number the greater resistance to kinking).	15 - 19	9 - 15
Instron test	85.25 +/- 43	125.2 +/- 47

Th haemocompatibility as d termined by the platel t consumption study using a closed loop system has been

enhanced in variation III. The lower the reading the more haemocompatible the surfac . Instr n testing exp ses th material to stretching forces. Variation III has greater strength, desirable in some non-vascular applications. Variation III demonstrates increased longitudinal stretch or elasticity (extension) and greater kink resistance required in a vascular prosthesis as it allows for better placement around the knee joint or other areas where curving is desirable as demonstrated in the human angiogram in Figure 10.

Animal studies undertaken with variation I, II and III in the aorto-iliac position in dogs to determine patency and long term performance have demonstrated excellent results (Table 2 below).

Table 2

In vivo studies comparing Variation I, II and III in the aorto-iliac position in the canine model.

Prosthesis type	no.of dogs	days patent	%patency
Variation 1	10	308 - 420	100%
	42	1 - 730	80%
Variation II	63	63 - >1460	87%
	47	365 - >1095	80.8%
Variation III	10	28 - 195	90%
	12	28 - 373	100%

Variation III demonstrates a thicker tissue cover on the flow surface and over the mesh bundles compared to variation II as Figures 11a and 11b, 12a and 12b and 13 show, indicating an improved flow surface and reducing the risk of prosthesis failure.

Variati n I, II and III hav been evaluated in human clinical studies for periph ral revascularisation in one

surgical centre and the results are shown in Figures 14a, 14b and 14c. The results obtain d at four years ar superior in Variation III with fewer occlusions occurring in the early time frame, thus documenting demonstrable enhancement in performance as a direct consequence of the modifications incorporated.

With reference to Figure 11, an explanted variation II prosthesis after seven months in the aorta-iliac position in the canine model is shown. Blood staining has occurred at th anastomoses (A) due to the thin tissue cover over the mesh on the flow surface (FS). The prosthesis was patent at explant. With reference also to Figure 11b, the flow surface (FS) is smooth and thrombus free however the tissue cover over the mesh (M) is thin.

Figure 12a and 12b shows that the same characteristics are present at seven months and four years in the canine model for variation II.

A variation III prosthesis in the canine model is shown after six months in the aorta-iliac position in Figure 13. The flow surface (FS) is thrombus free and the tissue cover over the mesh (M) is thick preventing the occurrence of blood staining.

Variations I, II and III have been evaluated in human clinical studies for peripheral revascularisation in one surgical centre and the results are shown in Figures 14a, 14b and 14c. The patency at 48 months for variation I is 32%. A large number of failures occurred in the first and second six month periods indicating a less than optimal flow surface to the prosthesis.

Figure 14b for variation II prosthesis shows little change from variati n I in the primary patency at the six and 48 m nth time period, though th s condary patency at the six

month period is satisfactory.

The primary and secondary patency of variation III prosthesis shown in Figure 14c indicates that the improvements in the technology for variation III have transferred to markedly improved clinical performance.

The results obtained at four years are superior in variation III with fewer occlusions occurring in the early time frame, thus documenting demonstrable enhancement in performance as a direct consequences of the modifications incorporated in variation III. The improvements in variation II are less dramatic.

The sheet form biomaterial is shown in Figures 15a and 15b, where a large-diameter variation III prosthesis was manufactured. The flat material was produced by cutting the tubular prosthesis along its length. Such a prosthesis can alternatively be manufactured in accordance with the third aspect of the invention by implanting in the host animal a sheet support and covering the sheet on both sides by the synthetic material, either in mesh form or alternatively in a painted particulate form.

Such prostheses produced from flat sheets by either method would be useful in non-vascular applications such as ligament replacement where strength is a critical consideration. Variations in shape and configurations are shown in Figure 16. Flat rectangular or oval shaped silicone, nylon, acrylic, polyethylene, teflon or polyurethane support sheets in isolation or in combination covered with synthetic mesh results in a bladder, pouch or pocket suitable for many applications (Figure 17, 18). The most important of them would be an application as a lining for artificial heart chambers. Unique features of an internal, smooth, haemocompatible surface shown in Figure 17 and external non-smooth surface shown in Figure 18 makes

this aspect of th invention extremely useful in applicati ns wher attachment to xt rnal surfaces and non-attachment of the internal surface is required, as for example in hernia repair (Figure 18).

Increased tissue cover obtained has transformed some disadvantages encountered in the original version into additional desirable features.

In US Patent 4,319,363, the prosthesis was stored in 90% absolute alcohol. This caused dehydration of the tissue component and necessitated rehydration prior to surgical implantation. In addition, in the original version, because of the thin tissue cover, with dehydration "cracking" occurred, often exposing the polyester through the tissue covering the flow surface, resulting in poor performance (Figure 19). The current version with increased tissue cover does not exhibit polyester at the flow surface.

In addition, during rehydration, instead of physiological saline, heparin is preferably used in th current invention and remains bioactive in the collagen/glutaraldehyde complex of the prosthesis enhancing performance. Tables 3 and 4 below show the results of heparin uptake studies. Heparin uptake studies. Heparin uptake and retention directly and following initial protamine sulphate treatment were studied. Heparin retention was assayed after 120 hours (5 days). Heparin uptake and retention were superior with PrSo4 treated grafts but it caused stiffness that made it less satisfactory. The direct method which consisted of partial dehydration resulted in a satisfactory prosthesis. Variation III that was tested, as claimed, can retain heparin in effective amounts opening the drug delivery potential in a controlled manner.

Table 3

^{3}H-heparin (cpm/m) in the lumen of graft segments

		^{3}H-HEPARIN IN LUMEN (cpm/ml) x 10^{6}						DIFFERENCE IN ^{3}H-HEPARIN CONCENTRATION AFTER FIVE DAYS (cpm/ml) x 10^{6}
GRAFT	BINDING PROCEDURE	INITIALLY			AFTER FIVE DAYS			
				AVERAGE			AVERAGE	
Var. III	Direct	3.04	3.17	3.10	1.49	1.52	1.51	1.59
Var. III	Protamine Sulphate	3.04	3.17	3.10	0.97	1.01	0.99	2.11

Table 4

^{3}H-heparin (cpm/cm^{2}) bound to graft segments.

GRAFT	BINDING PROCEDURE	^{3}H-HEPARIN BOUND TO GRAFT (cpm/cm^{2}) x 10^{6}		
				Average
Var. III	Direct	0.29	0.24	0.27
Var. III	Protamine Sulphate	0.26	0.25	0.26

The aldehyde and amino groups in the collagen/glutaraldehyde complex can not only retain heparin but other pharmacological agents like antibiotics eg tetracycline. The increased tissue cover combined with alcohol dehydration will enable the prosthesis to be moisture packed rather than fluid packed for end use.

The tanning procedure of the current invention is identical to that described in US Patent 4,319,363.

Variations may be made to current invention as would be apparent to a p rson skilled in th art of biomaterial

d sign similar to that d scribed in US Patent 4,319,363. These and other modifications may be made with ut departing from the ambient of the invention, the nature of which is to be ascertained from the foregoing description, figures and tables and the claims.

CLAIMS:

1. A biomaterial suitable for use in surgery in a human patient, comprising:

a coherent layer of non-human collagenous tissue which has been subjected to glutaraldehyde tanning so as to comprise cross-linked collagen fibrils, and

a reinforcement of synthetic material embedded within the coherent layer, said synthetic material having structure features for promoting said embedding the average density of said features being in situ greater than 50 per square centimetre.

2. A biomaterial as claimed in claim 1 wherein the density of said features is greater than 100 per square centimetre.

3. A biomaterial as claimed in claim 1 or claim 2 wherein the synthetic material is a fibre mesh and the features for promoting said embedding are the reticulations of the mesh.

4. A biomaterial as claimed in claim 3 wherein the mesh is embedded in the coherent layer such that the mesh structure is in a loose unstretched state.

5. A biomaterial as claimed in claim 3 wherein the fibre mesh is constructed from polyester yarn.

6. A biomaterial as claimed in claim 5 wherein the polyester yarn is augmented with polyurethane.

7. A biomaterial as claimed in claim 6 wherein the polyurethane is in the form of strands of the polyester dipped in polyurethane.

8. A biomaterial as claimed in claim 6 wherein the polyurethane is in the form of strands of polyurethane woven around strands of the polyester.

9. A biomaterial as claimed in claim 1 or claim 2 wherein the synth tic material is particulate in nature.

10. A biomaterial as claimed in claim 9 wherein said features are constituted by individual particles of that material.

11. A biomaterial as claimed in any one of claims 1 to 10 wherein the biomaterial is formed in the shape of a tube.

12. A biomaterial as claimed in any one of claims 1 to 10 wherein the biomaterial is in the form of a sheet.

13. A biomaterial as claimed in any one of the preceding claims wherein the biomaterial is smooth on one side to inhibit attachment to surfaces in the patient proximate said one side and rough on the other side to encourage said attachment.

14. A method of producing a biomaterial, comprising the steps of:

positioning a tubular synthetic fibre mesh structure about a support rod or tube;

implanting the mesh covered support rod or tube in the body of a living, non-human, host animal at such location as to cause growth of collagenous tissue thereon;

allowing said collagenous tissue to grow on the implant until there is formed a coherent wall of said tissue encompassing the rod or tube and having the mesh structure embedded therein;

removing the implant and said coherent wall of collagenous tissue from the body of the host animal;

subjecting said coherent wall of collagenous tissue to glutaraldehyde tanning in order to produce cross-linking of collagen fibrils therein so as to increase the strength of the wall and also to impart immunological inertness and sterility thereto; and

removing the rod or tube from within the coherent wall of collagenous tissue at any time subsequent to removal of the rod or tube and coherent wall of collagenous tissue from the body of the host animal;

wherein the tubular synthetic fibre mesh structure fits loosely over the support rod or tube.

15. A method as claimed in claim 14 wherein the tubular mesh is substantially larger in a longitudinal direction than the support rod or tube.

16. A method of producing a biomaterial, comprising the steps of:

implanting a sheet support in the body of a living, non-human, host animal at such a location as to cause growth of collagenous tissue thereon;

allowing said collagenous tissue to grow on the implant until there is formed a coherent layer of said tissue on both sides of the sheet support;

removing the implant and said coherent layer of collagenous tissue from the body of the host animal;

subjecting said coherent layer of collagenous tissue to glutaraldehyde tanning in order to produce cross-linking of collagen fibrils therein so as to increase the strength of the layer and also to impart immunological inertness and sterility thereto; and

separating the sheet support from the coherent layer of collagenous tissue at any time subsequent to removal of the implant from the body of the host animal to form a pocket, pouch or envelope of collagenous material.

17. A method as claimed in claim 16 wherein a synthetic material having structure features for promoting embedding of the synthetic material within the collagenous tissue is positioned on the support sheet so as to encompass both sid s of the support sheet.

18. A method as claimed in claim 17 wh r in the av rag density of said featur s in situ is greater than 50 per square centimetre.

19. A method as claimed in claim 18 wherein density of said features is greater than 100 per square centimetre.

20. A method as claimed in any one of claims 17 to 19 wherein the synthetic material is a fibre mesh and the features for promoting said embedding are the reticulations of the mesh.

21. A method as claimed in claim 20 wherein the mesh is embedded in the coherent layer such that the mesh structure is in a loose unstretched state.

22. A method as claimed in claim 20 wherein the fibre mesh is constructed from polyester yarn.

23. A method as claimed in any one of claims 17 to 22 wherein the biomaterial is smooth on one side to inhibit attachment to surfaces in the patient proximate said one side and rough on the other side to encourage said attachment.

24. A method a claimed in any one of claims 14 to 23 wherein the implant is made beneath the cutaneous muscle of the lateral thoracic wall of the host animal.

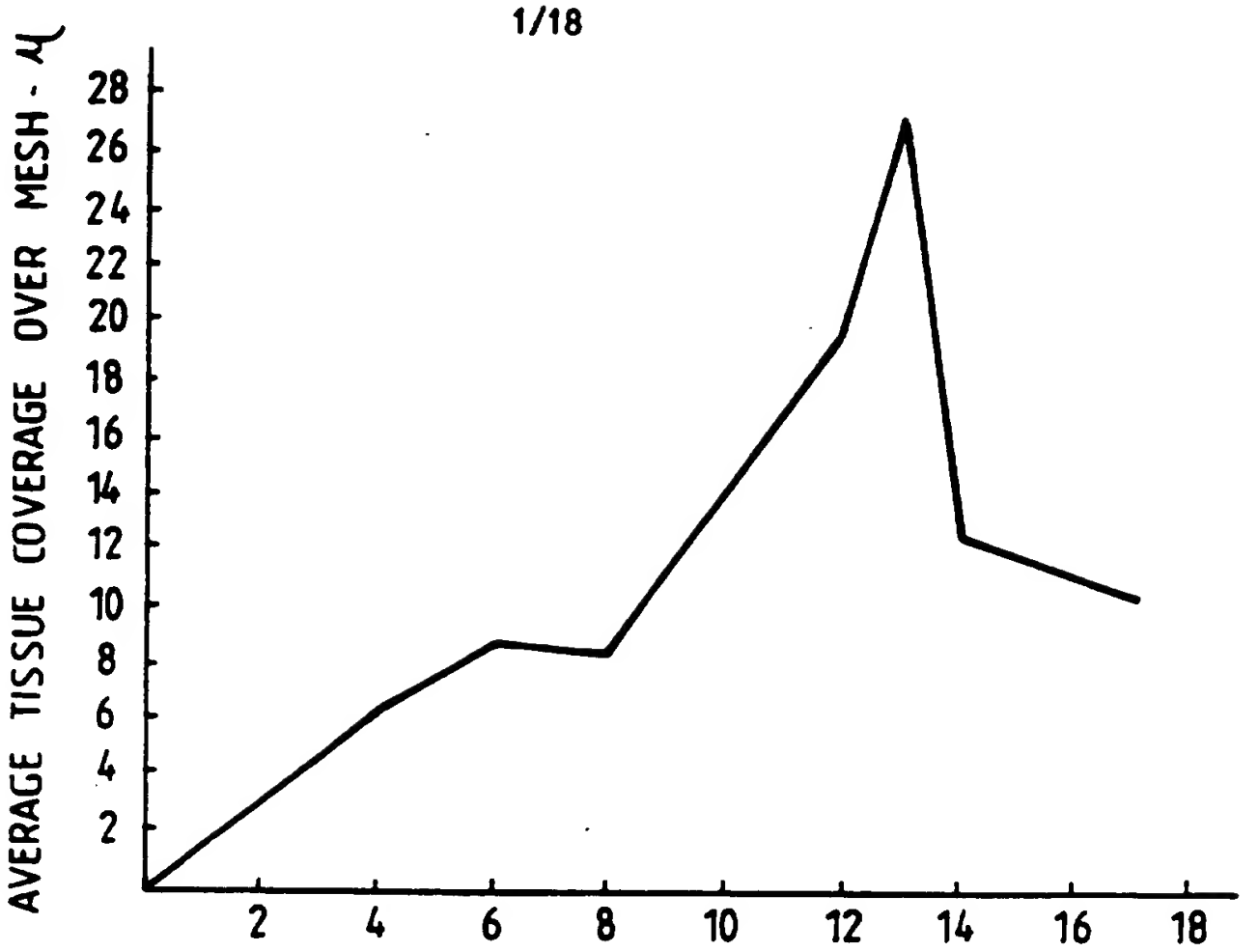
25. A method as claimed in any one of claims 14 to 23 wherein the host animal is a sheep.

26. A method as claimed in any one of claims 14 to 23 wherein the implant is allowed in the host animal for at least ten w eks.

27. A method as claimed in any one of claims 14 to 23

wherein the tanning step is carried out by immersing th implant and wall of tissue in a bath of buffered glutaraldehyde after removal of the body of the host animal and before removal of the support or tube.

28. A method as claimed in any one of claims 14 to 23 wherein the biomaterial is rehydrated for use using heparin.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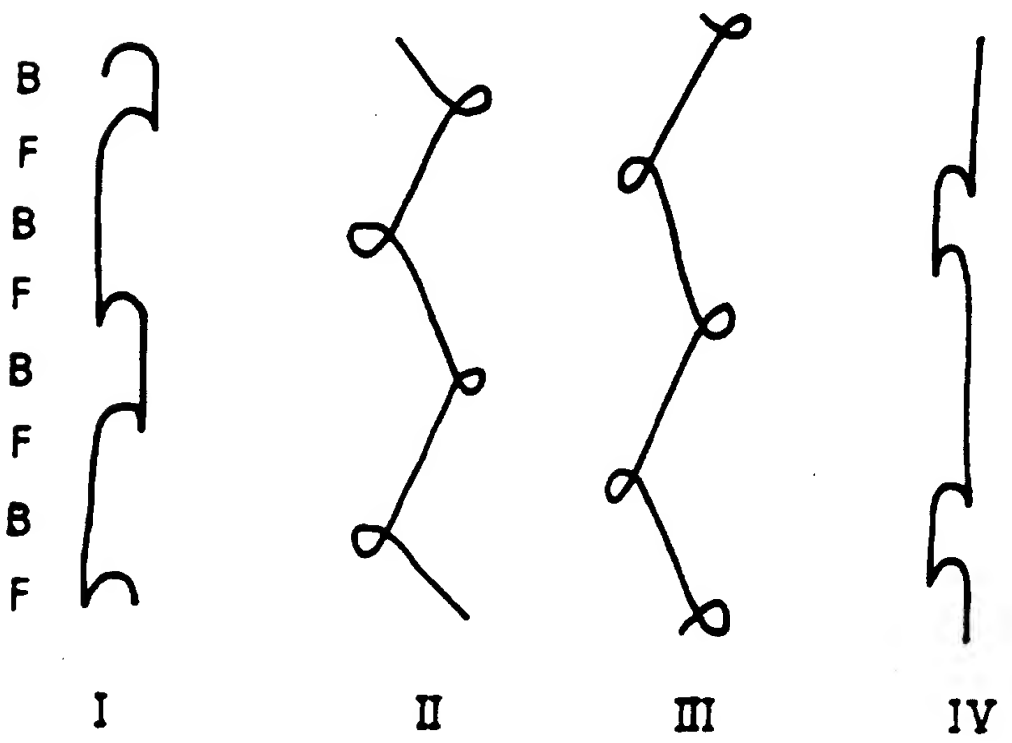
GROWTH TIME (Weeks)

FIG. 1.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IV

FIG. 2a.

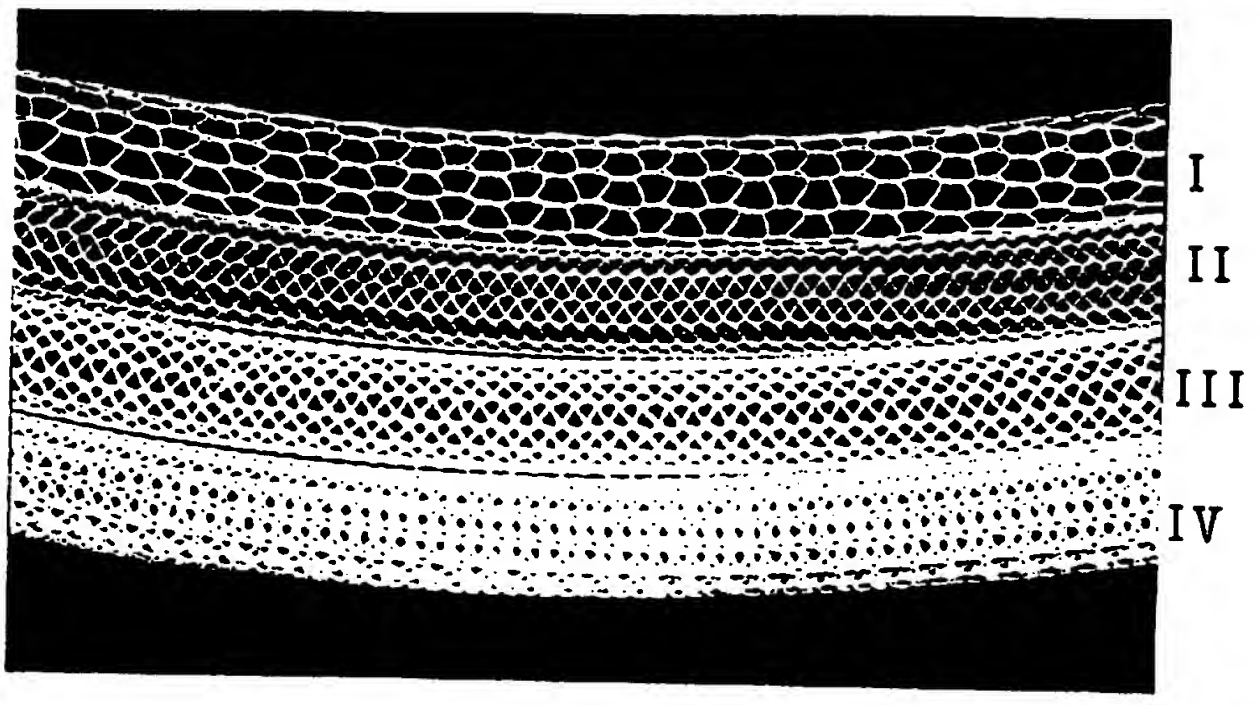

Fig. 2

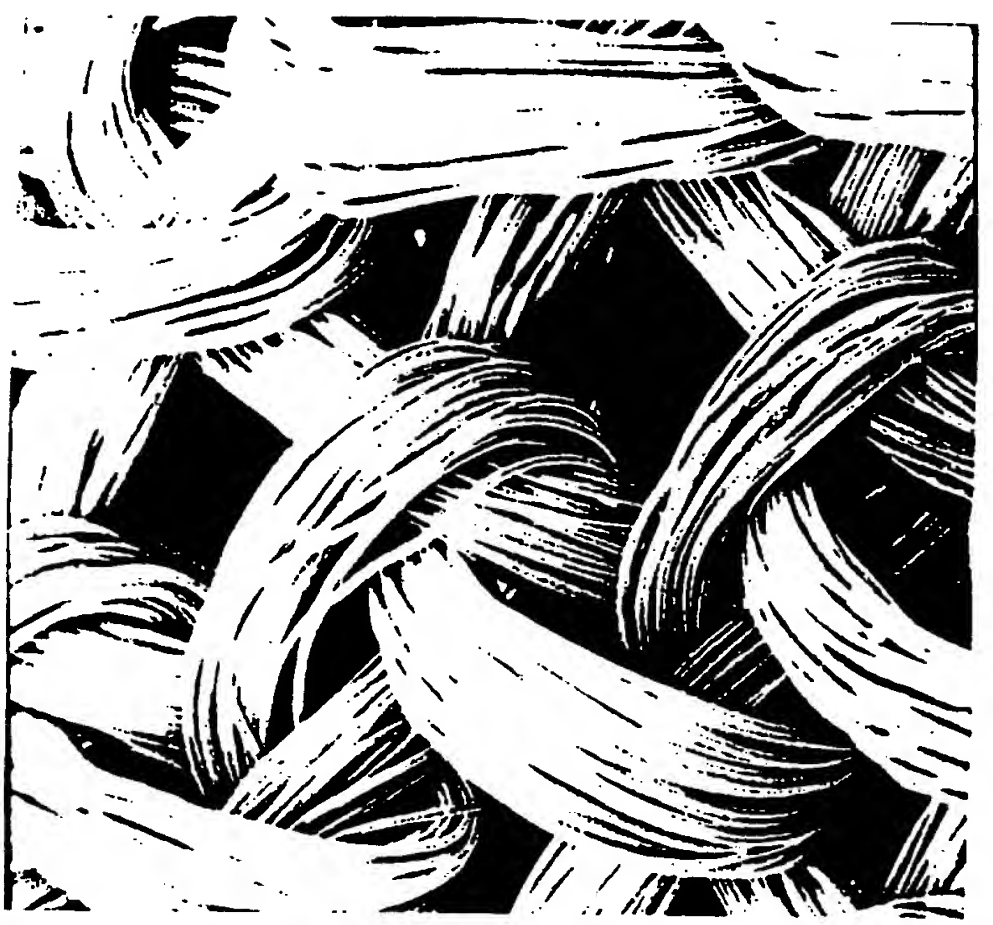

Fig. 3

Fig. 4

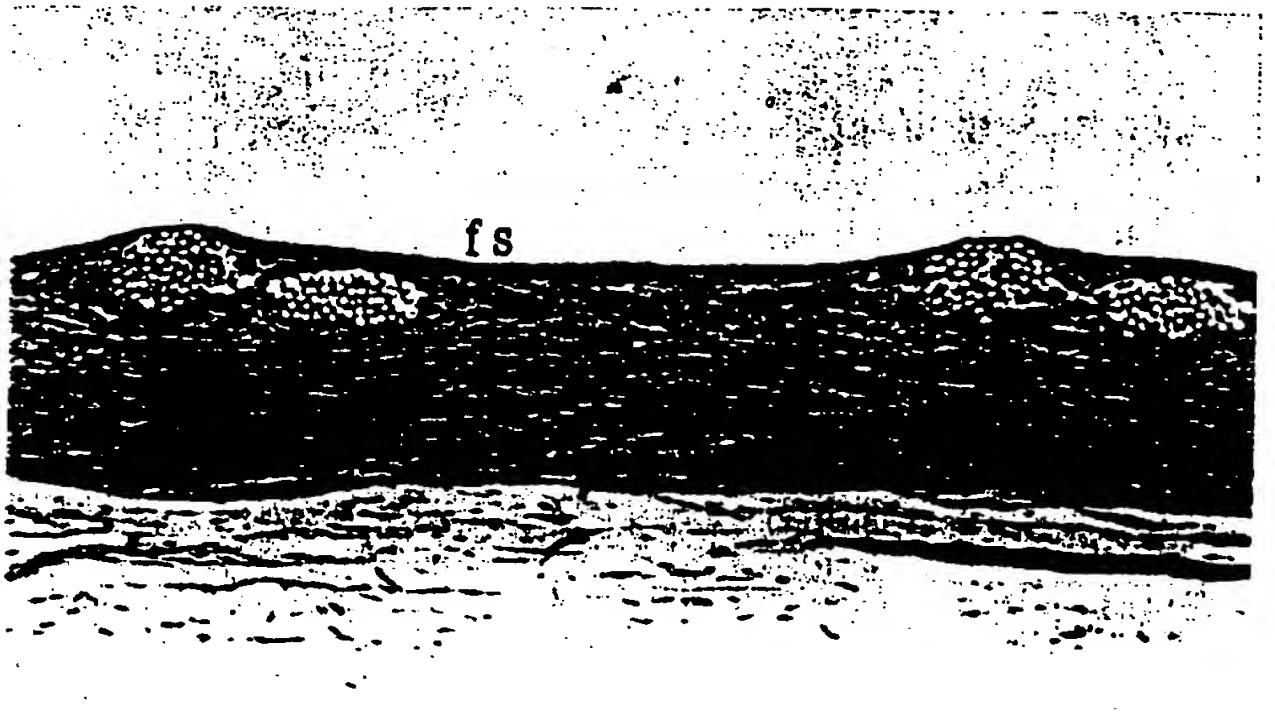

Fig. 5

Fig. 6

Fig. 7

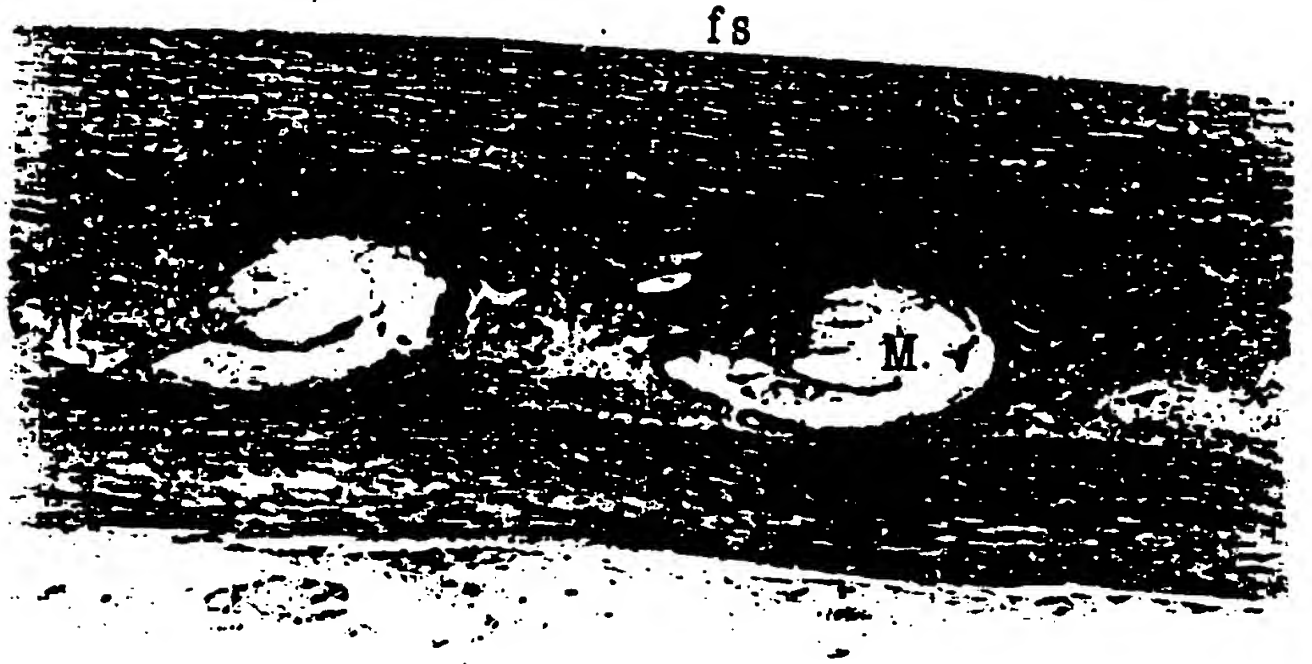

Fig. 8


fs

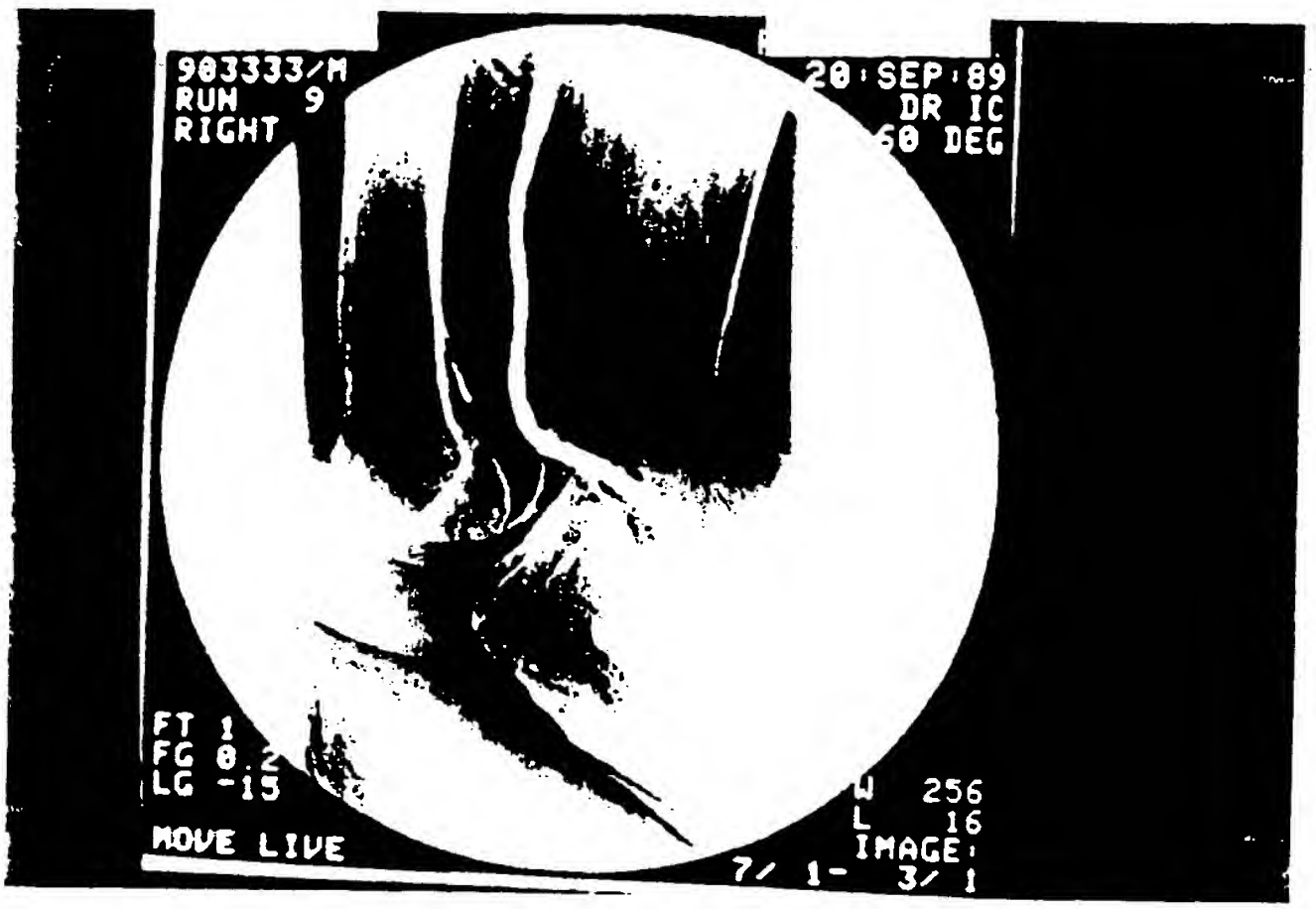
90333/M
RUN 9
RIGHT
20 SEP 89
DR IC
60 DEG
FT 1
FG 0.2
LG -15
MOVE LIVE
W 256
L 16
IMAGE
7/ 1- 3/ 1

Fig. 10

Fig. 11a

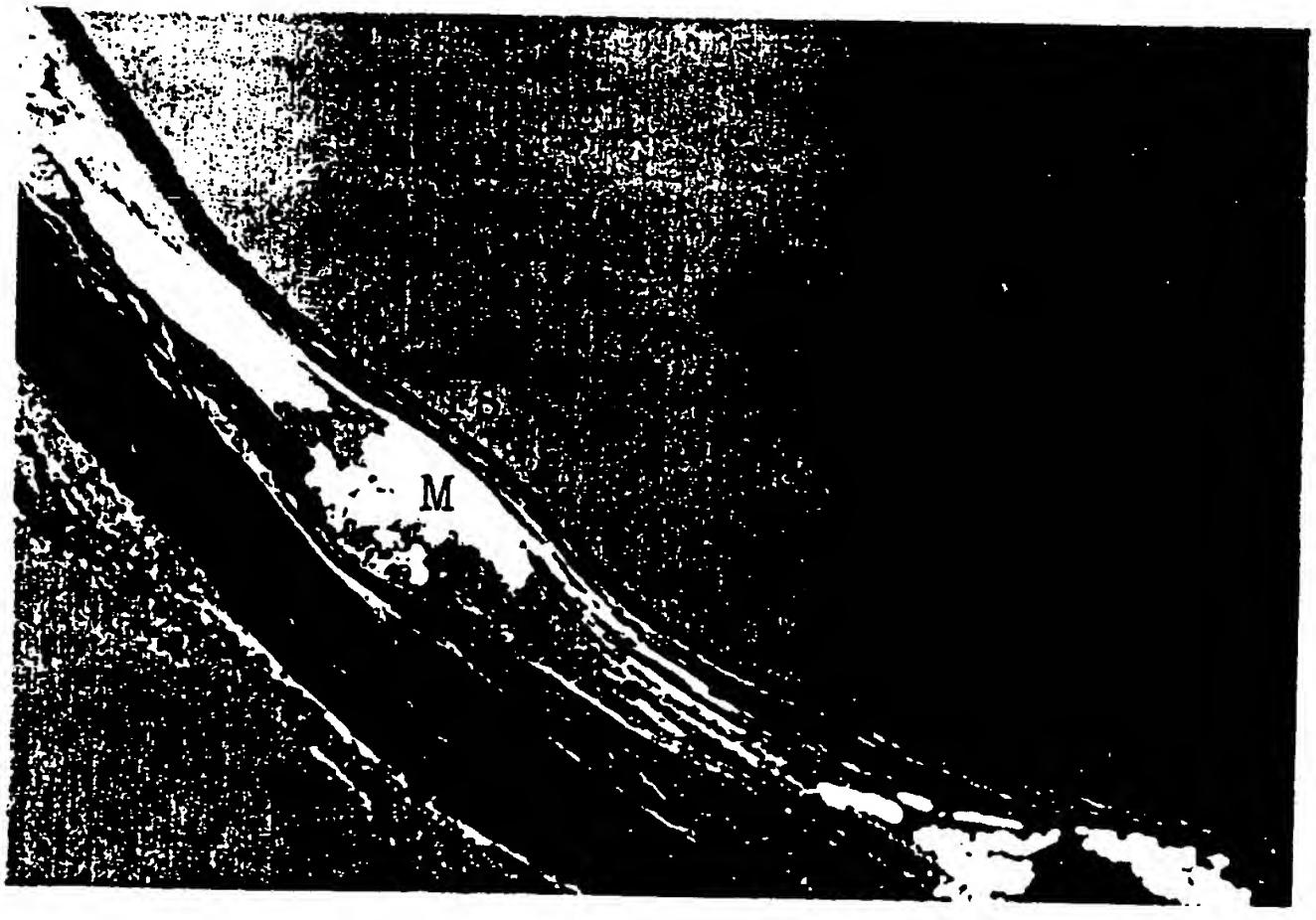

Fig. 11b

Fig. 12a

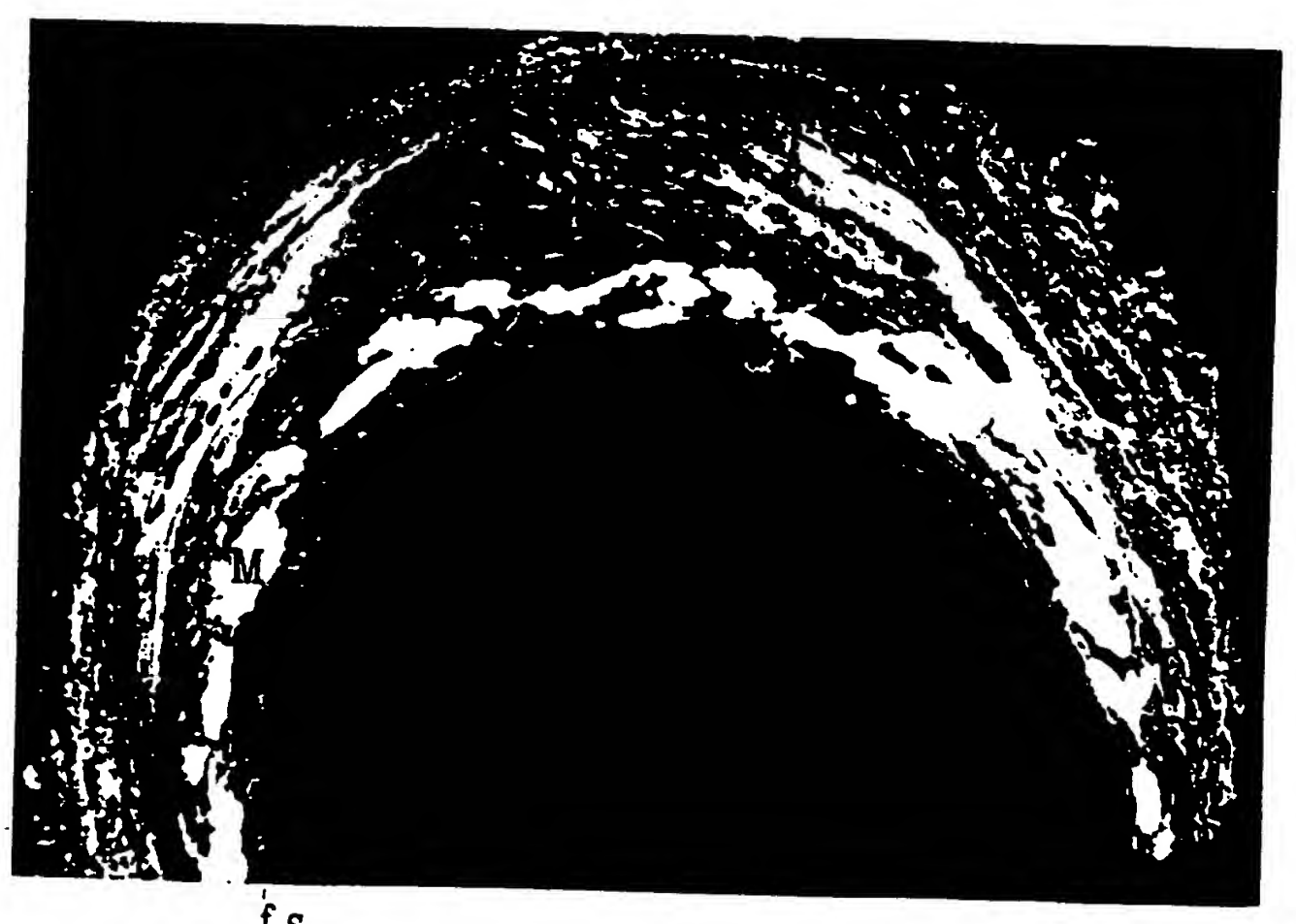

Fig. 12b

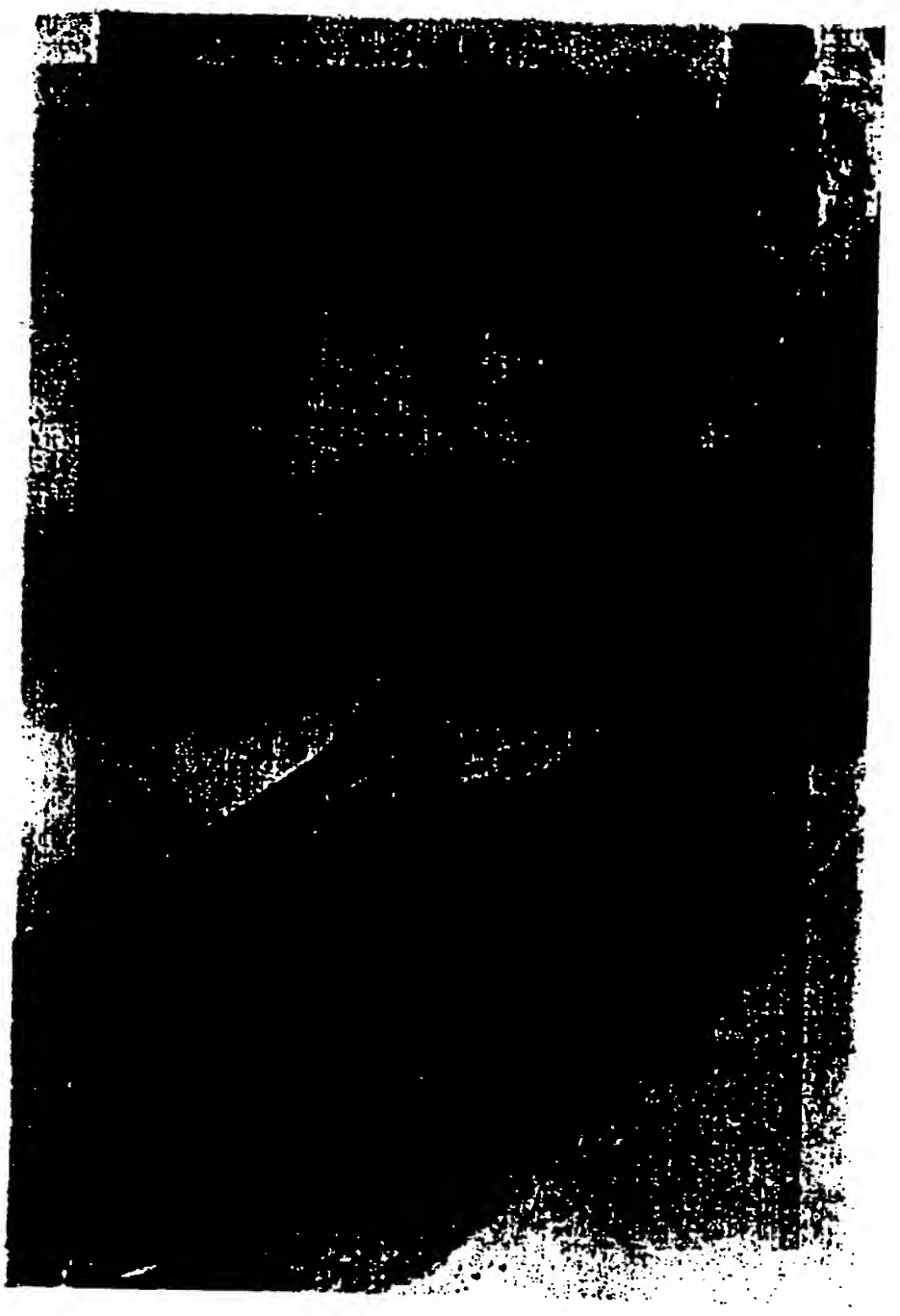

Fig. 13

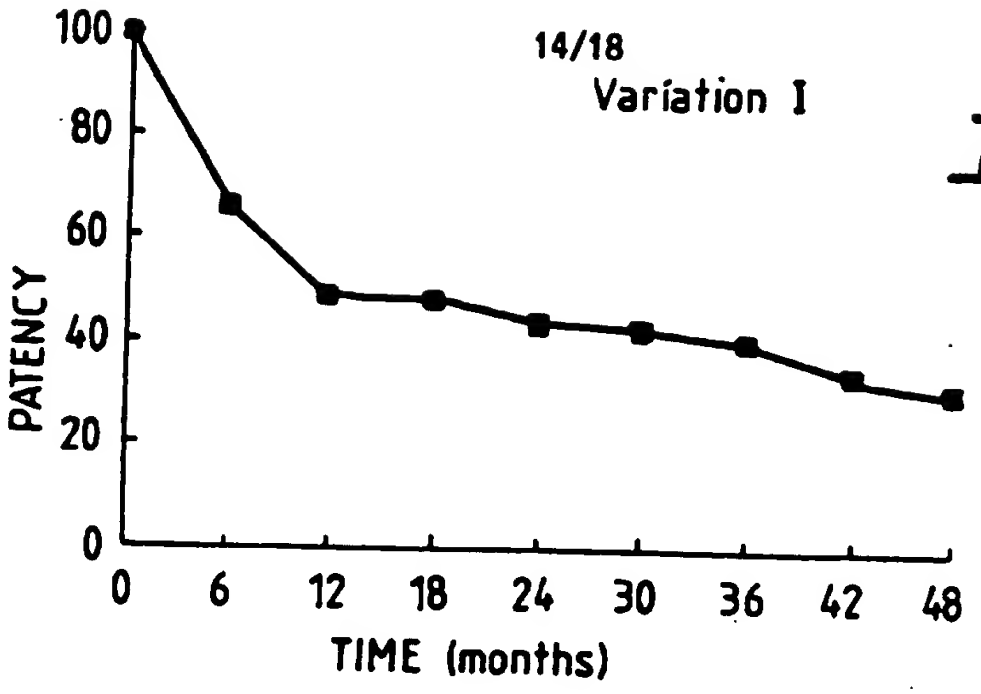

FIG. 14a

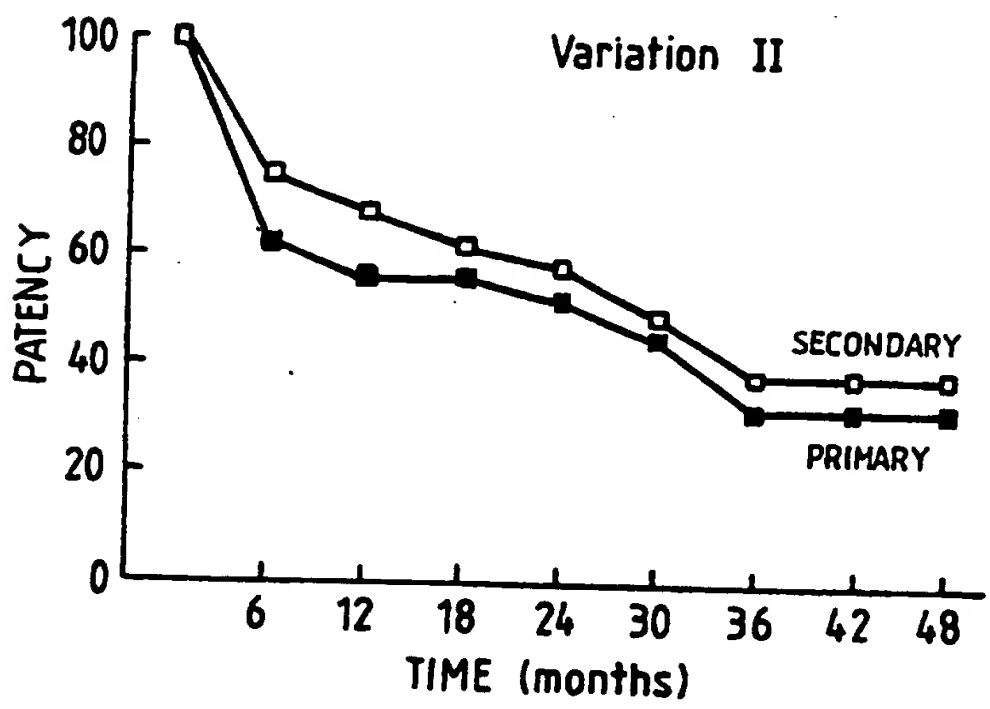

FIG. 14b

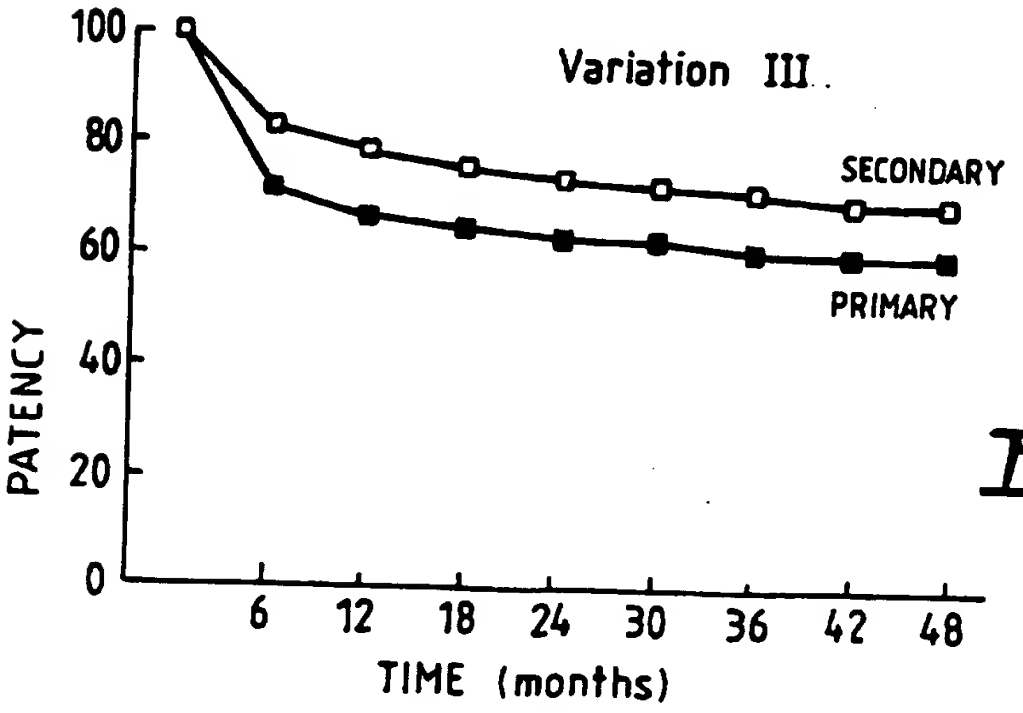

FIG. 14c

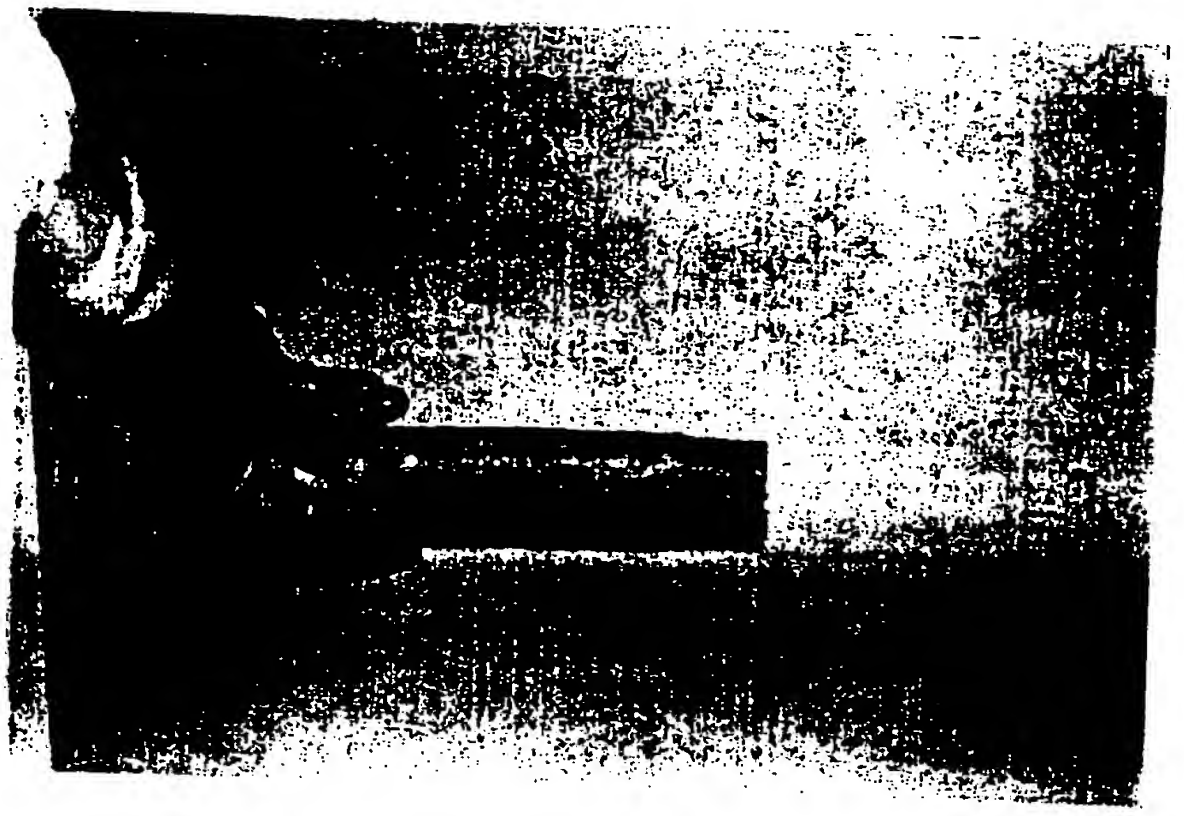

Fig. 15a

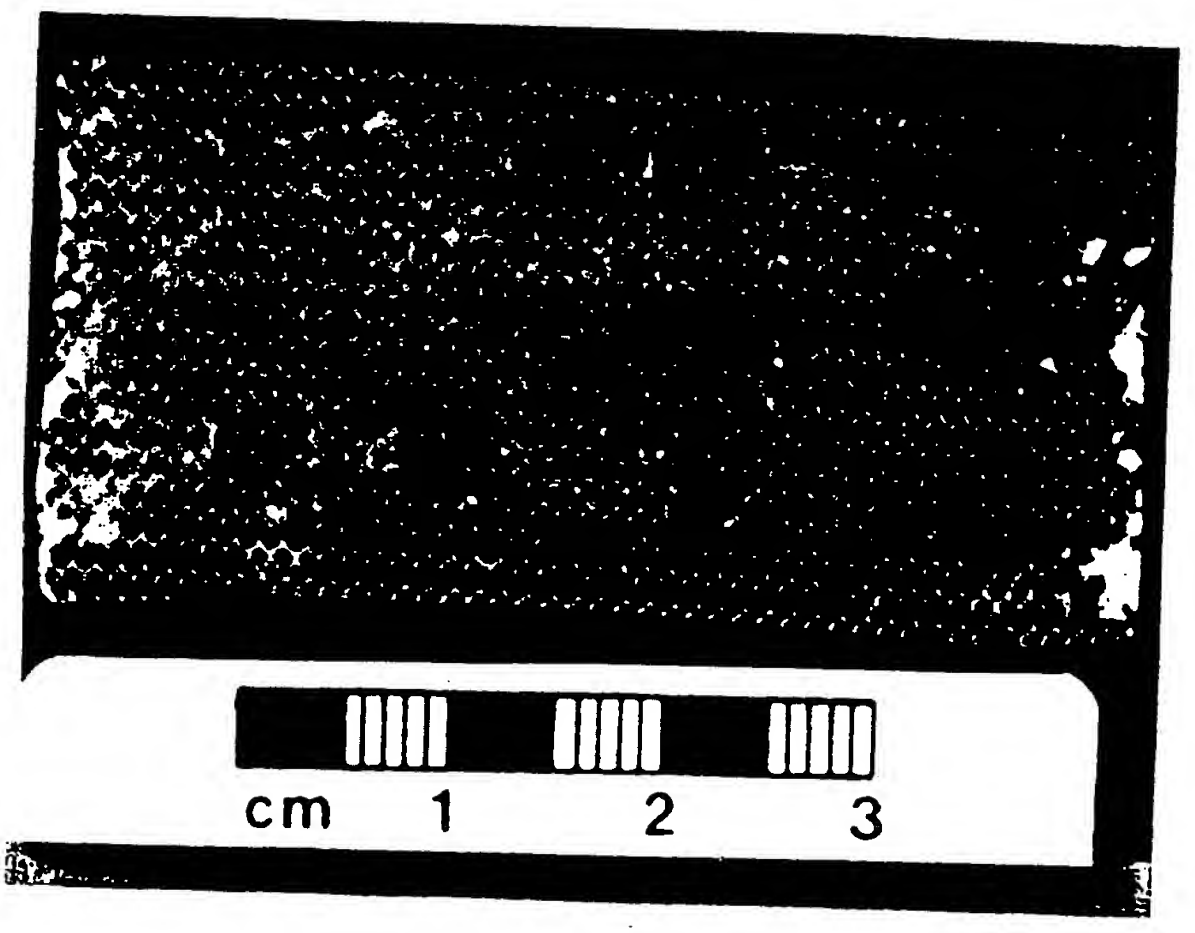

Fig. 15b

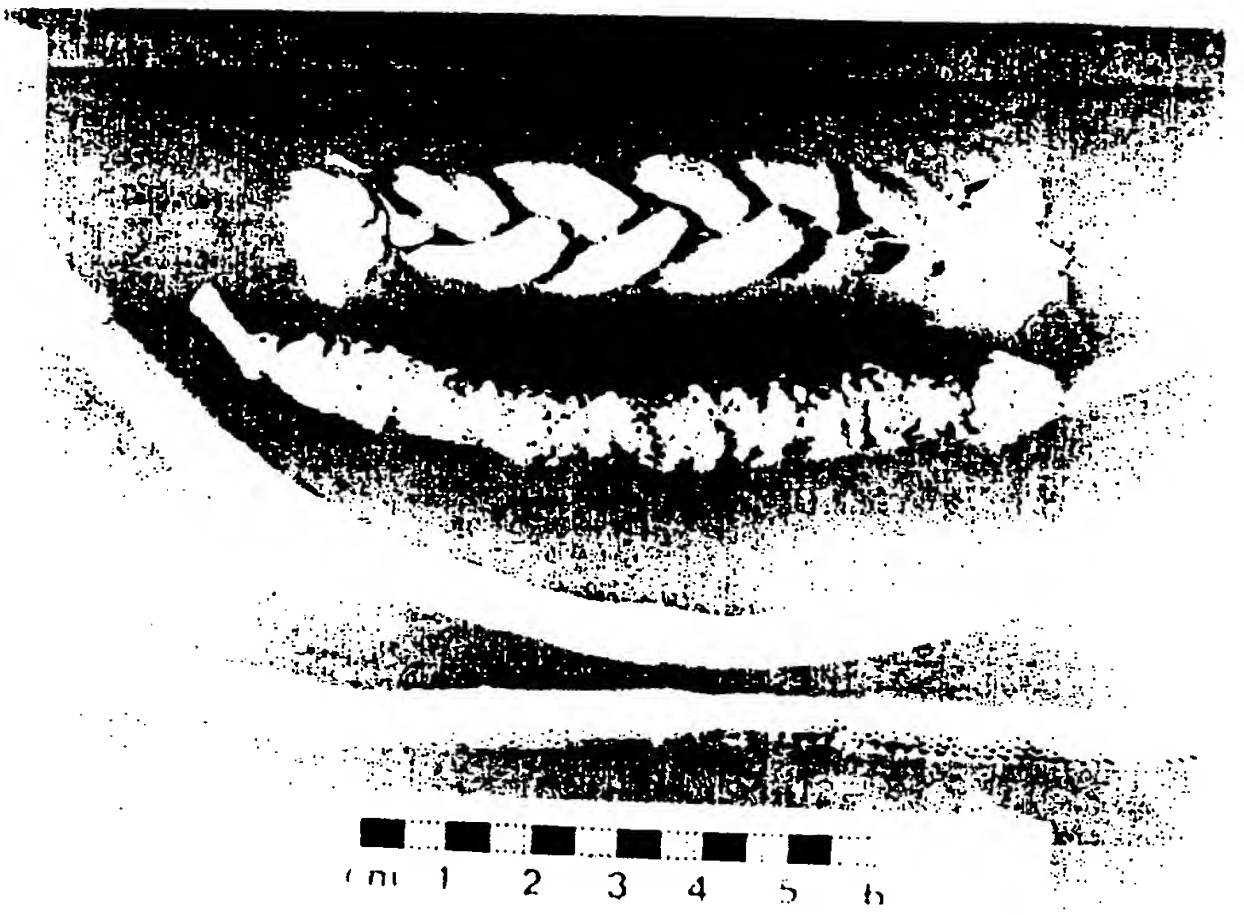

Fig. 16

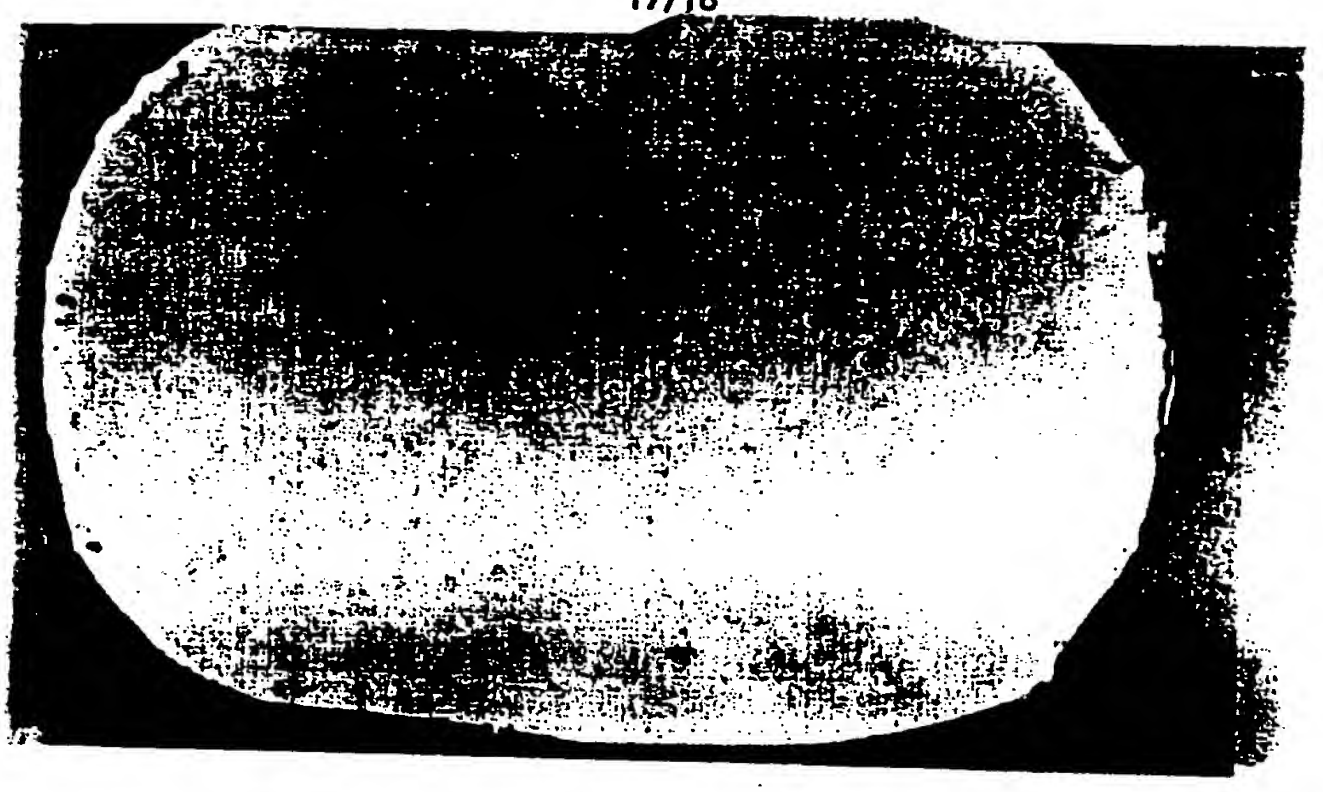

Fig. 17

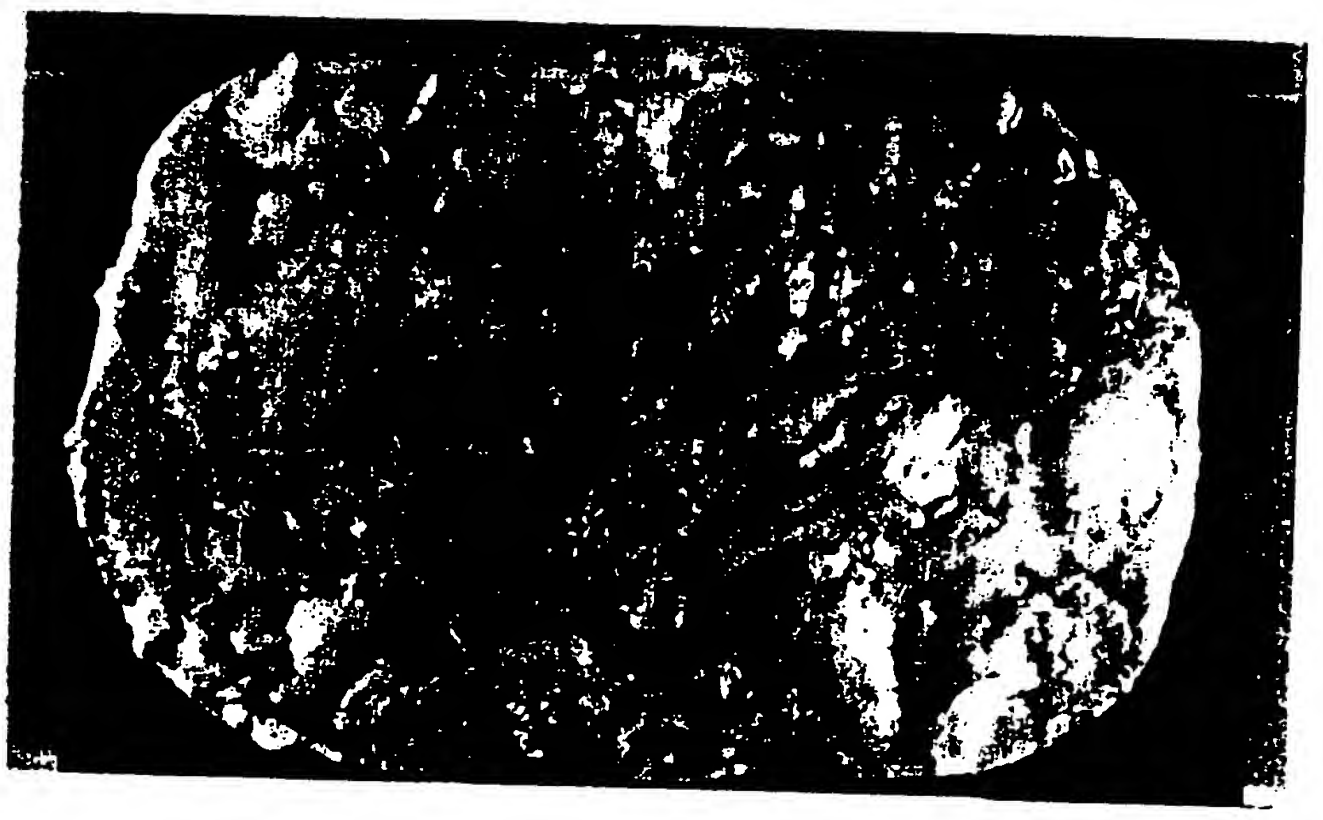

Fig. 18

Fig. 19

INTERNATIONAL SEARCH REPORT

International Application No.
PCT/AU 96/00126

A. CLASSIFICATION OF SUBJECT MATTER

Int Cl[6]: A61L 27/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
Int Cl[6]: A61L 27/00

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
DERWENT A61L 27/00 * COLLAGEN

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,Y	AU 60596/86 A (LAUREN) 29 January 1987 Pages 3, 7-13, claims 1, 4, 5, 7	1, 2, 11-13
Y	US 5002583 A (PITARU et al) 26 March 1991 Entire document	1-13
X	AU 58305/86 (590573) B (THOMAS JEFFERSON UNIVERSITY) 11 December 1986 Pages 12-25. Claims, Figures 1-3	1-28

[X] Further documents are listed in the continuation of Box C

[ ] See patent family annex

* Special categories of cited documents:

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

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Date of the actual completion of the international search
24 April 1996

Date of mailing of the international search report
09 MAY 1996

Name and mailing address of the ISA/AU
AUSTRALIAN INDUSTRIAL PROPERTY ORGANISATION
PO BOX 200
WODEN ACT 2606
AUSTRALIA Facsimile No.: (06) 285 3929

Authorized officer
Grant McNeice
GRANT McNEICE
Telephone No : (06) 283 2055

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INTERNATIONAL SEARCH REPORT

International Application No.
PCT/AU 96/00126

C (Continuation) **DOCUMENTS CONSIDERED TO BE RELEVANT**

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 4553974 A (MAYO FOUNDATION) 19 November 1985 Columns 3-14	1-4, 11-13
Y	AU 53379/90 (637605) B (REGEN CORPORATION) 26 September 1990 Pages 13-18, claims 1-5, 11-16, 20-25	1-4
X	AU 69085/91 (BIOSYNTHESIS INC) 27 June 1991 Pages 5-16, Claims 1-10	1-28
X	US 4319363 A (VETTIVETPILLAI KETHARANATHAN) 16 March 1982 Columns 1-14	1-28

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application N .
PCT/AU 96/00126

This Annex lists the known "A" publication level patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document Cited in Search Report		Patent Family Member					
AU	60596/86	US	4755593				
US	5002583	DE	3627316	FR	2590175	GB	2178963
		IL	76079				
AU	58305/86	AT	113850	BR	8602659	CA	1293700
		DE	3650134	EP	206025	EP	518389
		EP	206025	ES	555739	ES	8900149
		IL	78950	JP	62049857	MX	165125
		US	4820626	ZA	8603958	US	5131907
		US	5194373	US	5035708	US	5230693
		US	5312380	US	5372945	US	5441539
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		ZA	8506106				
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		DE	69021204	EP	461201	JP	4504968
		WO	9009769	US	5108438	US	5258043
		US	5306311	US	5116374	US	5158574
		US	5263984	AT	87452		
AU	69085/91	CA	2070294	EP	504262	JP	5502178
		WO	9108718				
US	4319363	AU	47208/79				

END OF ANNEX